AMENDMENTS TO THE SPECIFICATION

In the specification, please replace the paragraphs spanning p. 7, l. 27 through p. 10, l. 1 with the following amended paragraphs:

~~**Brief Description of the Drawings**~~

Certain embodiments of the invention are described, below: ~~reference being made to the accompanying drawings, wherein:~~

~~Figure 1 shows the~~ The water-maze performance of ~~TgCRND8 mice tested at 11 weeks of age~~. The TgCRND8 mice (n = 5) had significantly longer escape latencies ~~(Panel A)~~ and search paths ~~(Panel B)~~ than their non-Tg littermates (n = 8), ($F(1,10) = 28.8$, $p < 0.001$ and $F(1,10) = 22.0$, $p < 0.01$, respectively), and consequently dwelled significantly less ($F(1,10) = 14.9$, $p < 0.01$) in the target quadrant (TQ) containing a hidden platform ~~(Panel C)~~. The locomotor abilities assessed by the speed of swimming ~~(Panel D)~~ between Tg and non-Tg mice were comparable ($F(1,10) = 0.48$, $p > 0.05$).

The TgCRND8 mice showed impaired spatial memory for the platform position as measured by their search patterns during 60 seconds swim in the probe trial when the hidden platform was removed from the pool. They showed a tendency to search the TQ less ~~(Panel E)~~ and crossed the exact annulus of the platform position significantly less often ($t(10) = 2.1$, $p = 0.06$) than non-Tg mice~~(Panel F)~~.

~~Figure 2 shows the~~ The water-maze performance of bi-transgenic TgCRND8 x TgPS2(M239V)1379 mice was tested. When tested at 2 months of age, the bi-transgenic mice (n = 5) had significantly longer ($F(1,11) = 8.1$, $p< 0.05$, with the effect size due to the genotype (η^2) = 42%) escape latencies ~~(Panel A)~~ and the search path($F(1,11) = 8.46$, $p < 0.05$, $\eta^2 = 43\%$), ~~(Panel B)~~ than the single Tg PS2(M239V)1379 littermates (n = 8). During immediately following learning reversal test when the hidden platform was moved to the opposite quadrant to the original TQ, the bi-transgenic mice showed a tendency to longer escape latencies ($F(1,11) = 3.28$, $p = 0.1$, $\eta^2 = 23\%$~~, Panel C~~) but their search paths ~~(Panel D)~~ did not differ significantly from the single TgPS2(M239V)1379

mice ($F(1,11) = 2.46$, $p > 0.05$, $\eta^2 = 18\%$). The swim speed of the mice in both transgenic groups was comparable during the tests.

When re-tested at 5 months of age, the bi-transgenic mice showed significantly longer ($F(1,10) = 16.6$, $p < 0.01$, $\eta^2 = 62\%$, (1 bi-transgenic mouse died)) escape latencies ~~(Panel E)~~ and significantly longer search paths ($F(1,10) = 20.3$, $p < 0.001$, $\eta^2 = 66\%$~~, Panel F~~) than the single Tg PS2(M239V)1379 littermates. This significant impairment was due to the initial poor performance of bi-transgenic mice in the tests (group × days interactions: $F(2,40) = 3.32$, $p < 0.05$ for latency and $F(2,40) = 2.85$, $p = 0.07$ for path) This impairment in learning acquisition persisted in the reversal tests when the bi-transgenic mice still showed significantly longer latencies ($F(1,10) = 28.58$, $p < 0.001$, $\eta^2 = 74\%$ ~~Panel G~~) and longer search paths ($F(1,10) = 27.43$, $p < 0.001$, $\eta^2 = 73\%$ ~~Panel H~~) then single Tg littermates. Although the mice eventually improved their performance at the end of learning reversal training, the group × days interactions for both measures did not reach significance at $\alpha = 0.05$.

~~Figure 3 shows the~~ The water maze performance of TgCRND8 mice (Tg(APP)8); n = 12) and non-transgenic littermates (non-Tg; n = 20) immunised with Aß42 and TgCRND8 mice (Tg(APP)8; n = 9) and non-transgenic littermates (non-Tg;n=19) immunised with IAPP-peptide was tested. The immunisation with the $A\beta_{42}$ peptide significantly reduced cognitive deficit in TgCRND8 mice as measured by their escape latency and the search path as compared to non-Tg littermates. Although the Aß42-immunised TgCRND8 mice showed overall longer escape latencies ~~(Panel A)~~ and search paths ~~(Panel C)~~, ($F(1,30) = 9.71$, $p < 0.01$; $F(1,30) = 10.9$, $p < 0.01$ for latency and path respectively) than non-Tg mice, the difference was due to their initial longer searches (group × day interactions: $F(4,120) = 2.83$, $p < 0.05$ - latency; $F(3,120) = 4.73$, $p < 0.01$ - path). The comparisons of their performance during the last 3 days of training did not reveal significant differences between the groups ($F(1,30) = 0.64$, $p > 0.05$ - latency; $F(1,30) = 1.24$, $p > 0.05$ - path). The Aß42-immunised Tg mice showed a slight tendency to search the TQ less ($F(1,30) = 3.71$, $p = 0.06$~~, Panel E~~), but their swim speed did not differ significantly from non-Tg mice ($F(1,30) = 1.33$, $p > 0.05$) ~~(Panel G)~~.

The IAPP immunised TgCRND8 mice showed significantly longer escape latencies ~~(Panel B)~~ and search paths ~~(Panel D)~~ than their non-Tg littermates ($F(1,26) = 39.9$, $p < 0.001$ - latency; $F(1,26) = 43.9$, $p < 0.001$ - path). Although they did not differ in their initial search from nonTg mice, they did not improve their performance during training (group × day interactions: $F(4,104) = 6.31$, $p < 0.001$ - latency, $F(4,104) = 5.69$, $p < 0.001$ - path). They also spent significantly less time searching the target quadrant ($F(1,26) = 7.39$, $p < 0.05$~~, Panel F~~), but their swim speed was not affected by the immunisation ($F(1,26) = 1.73$, $p > 0.05$~~, Panel H~~).

In the specification, please replace the paragraph at p. 12, ll. 7-9 with the following amended paragraph:

TgCRND8 mice exhibit deficits in spatial learning, as assessed by the hidden-platform version of the Morris water-maze. These deficits, measured against control non-transgenic littermates, can be detected as early as 11 weeks of age ~~(Figure 1)~~.

In the specification, please the paragraphs at p. 14, ll. 10-28 as follows:

TgCRND8 mice were crossed with transgenic mice which over-express mutant human presenilin (PS1 or PS2) transgenes (Table 2). A potent increment in plaque density was noted in TgCRND8 mice which co-express a human mutant presenilin transgene denoted TgPS1(L286V)1274 (which carries a familial Alzheimer disease (FAD) mutation). Thus, in TgCRND8 x TgPS1(L286V)1274 mice, an amyloid burden closely resembling the postmortem AD brain is already present by 62 days of age ~~(Figure 1A: compare with TgCRND8 mice at 117 days of age in Panel C)~~.

In a similar manner, crossing TgCRND8 mice with mice carrying the FAD mutant form of presenilin 2 (a methionine to valine mutation at amino acid residue 239 of the PS2 gene coding region) also results in a potent increment in plaque density. ~~A comparison at age 91 days of TgCRND8 and TgCRND8 x TgPS2(M239V) mice (where the PS2 transgene line is designated 1379) is shown in Figure 2.~~

A still greater enhancement was obtained by crossing TgCRND8 mice with mice bearing a human mutant presenilin transgene with two FAD mutations in *cis* to each other - denoted Tg(M146L+L286V)6500. In TgCRND8 x TgPS1(M146L+L286V)6500 mice, hippocampal amyloid deposits were detectable by 30 days of age ~~(Figure 3)~~, which is 5 months earlier than previously reported for any other double APP/PS1-Tg mice (which typically develop plaques at or after 6 months of age) (22, 23).

In the specification, please replace the paragraph at p. 15, ll. 8-11 with the following amended paragraph:

A progressive deterioration in cognitive performance beginning at age 8-10 weeks has also been seen in bi-transgenic mice generated by crossing TgCRND8 mice with mice expressing an FAD allele of presenilin 2 (TgPS2(M239V), line 1379 ~~(Figure 5)~~.

In the specification, please replace the paragraph at p. 23, ll. 7-21 with the following amended paragraph:

Spatial learning was assessed in TgCRND8 mice using a well-established paradigm, the Morris water maze (31) as described (32). The analysis of behaviour of TgCRND8 mice revealed a significant cognitive deficit in their acquisition of spatial information assessed in the place discrimination (hidden platform in the same spatial position) version of a water maze as early as 11 weeks of age. During training, the mice showed a significantly slower learning rate reflected by their longer escape latencies and search paths as well as chance level search of the quadrant containing the hidden platform ~~(Fig. 1)~~. The TgCRND8 mice also showed spatial memory deficit when tested in the probe trail. During this trial, the hidden platform was removed and mice were allowed to search for its position for 60 seconds. While the non-Tg mice showed clear, selective spatial bias for the platform position ~~(Fig. 1, E and F)~~, the search of TgCRND8 mice was more generalised and included adjacent to TQ quadrants, and crossed the annulus of the platform position significantly less then non-Tg littermates. The swimming abilities of both APP positive and non-Tg mice were comparable during testing, thus did not bias the measures of learning.

In the specification, please replace the paragraph at p. 25, ll. 3-18 with the following amended paragraph:

TgCRND8 x TgPS2(M239V)1379 bi-transgenic mice were tested at 2 months of age and showed a significant cognitive defect in spatial learning acquisition with the effect size in the range of 40% ~~(Figure 2, panels A & B)~~. During the following reversal test, however, although inferior at the beginning, the bi-transgenic mice showed comparable performance by the end of the test (about 20% of variance explained by the transgenotype) ~~(Figure 2, panels C & D)~~. During the re-test at 5 months of age, the same bi-transgenic mice showed highly significant learning deficit during acquisition and reversal test (effect size due to transgenotype of 60% and 70% respectively) ~~(Figure 2, Panels E & F)~~. Also, the bi-transgenic mice did not differ from TgPS2(m239V)1379 mice in their swim speed at any age tested. Expression of mutated human APP in the presence of mutated PS2 gene confers impairment in spatial learning and memory as early as 2 months of age, as compared to the performance of TgPS2(M239V)1379 mice which behave in a manner similar to non-transgenic mice derived from the same combination of inbred strains. This impairment progresses with age and by the age of 5 months, the mice show constant deficiency in acquiring new spatial information.

In the specification, please replace the paragraphs spanning p. 26, l. 10 through p. 27, l. 11, with the following amended paragraphs:

~~As seen in Figure 3, the~~ Immunisation with Aβ42 peptide attenuated the cognitive impairment of TgCRND8 mice at early stages of immunisation. The water maze performance of TgCRND8 mice immunised with $A\beta_{42}$ or 1APP (immunisation commenced at 6 weeks of age) was tested at 11 weeks of age. The immunisation with the $A\beta_{42}$ peptide significantly reduced cognitive deficit in TgCRND8 mice as measured by escape latency ~~(Panel A)~~ and search path length ~~(Panel D)~~ as compared to non-Tg littermates. Although the Aβ42 immunised TgCRND8 mice showed overall longer escape latencies ~~(Panel A)~~ and search paths ~~(Panel D)~~, ($F(1,30)=9.71$, $p<0.01$; $F(1,30)=10.9$, $p<0.01$ for latency and path respectively), than non-Tg mice, the difference

was due to their initial longer searches (group x day interactions: $F(4,120)$-2.83, $p<0.05$ – latency; $F(3,120)=4.73$, $p<0.01$ – path). The comparisons of their performance during the last 3 days of training did not reveal significant differences between the groups ($F(1,30)=0.64$, $p>0.05$ – latency; $F(1,30)=1.24$, $p>0.05$ – path). The Aβ42 immunised TgCRND8 mice showed a slight tendency to search the TQ less ($F(1,30)=3.71$, $p = 0.06$, ~~panel E~~), but their swim speed ~~(Panel G)~~ did not differ significantly from non-Tg mice ($F(1,30)=1.33$, $p>0.05$). The IAPP immunised TgCRND8 mice showed significantly longer escape latencies ~~(Panel B)~~ and search paths ~~(Panel C)~~ than their non-Tg littermates ($F(1,26)=39.9$, $p<0.001$ – latency; $F(1,26)=43.9$, $p<0.001$ – path). Although the transgenics did not differ in their initial search from nonTg mice, they did not improve their performance during training (group x day interactions: $F(4,104)=6.31$, $p<0.001$ – latency, $F(4,104)=5.69$, $p<0.001$ – path). They also spent significantly less time searching the target quadrant ($F(1,26)=7.39$, $p<0.05$~~, panel F~~), but their swim speed was not affected by the immunisation ($F(1,26)=1.73$, $p>0.05$~~, panel H~~).

In summary, the immunisation of TgCRND8 mice with Aβ42 peptide at 6 weeks followed by a boost at 8 weeks, significantly improved the cognitive abilities of TgCRND8 mice in the water maze paradigm administered at 11 weeks of age. On the other hand, the mice immunized with IAPP showed significant impairment in acquisition of spatial information as compared to non-Tg littermates ~~(Figure 3)~~, and this impairment was of a similar nature to that seen in non-immunised TgCRND8 mice ~~(data not shown)~~.